

The Role of the Skin Barrier in Periorificial Dermatitis

Anamaria Balić¹, Domagoj Vlašić², Mislav Mokos², Branka Marinović¹

¹Department of Dermatology and Venereology, University Hospital Centre Zagreb, School of Medicine University of Zagreb, Zagreb, Croatia; ²University of Zagreb, School of Medicine, Zagreb, Croatia

Corresponding author:

Professor Branka Marinović, MD, PhD
Department of Dermatology and Venereology
University Hospital Centre Zagreb
School of Medicine University of Zagreb
10000 Zagreb
Croatia
branka.marinovic@kbc-zagreb.hr

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ABSTRACT Periorificial dermatitis, mostly known as perioral dermatitis, is a benign inflammatory facial dermatosis which can be a severe burden and even disfiguring and psychologically disturbing. The disease still presents a challenge for physicians when it comes to etiology and appropriate therapy. Although a variety of extrinsic and intrinsic factors have been proposed as etiopathogenetic factors, none of these fully explain complex pathogenesis of the disease. There is more evidence that supports beliefs that the epidermal barrier dysfunction is an underlying main pathogenic factor that contributes to persistent cutaneous inflammation in typical facial localizations. Patients with periorificial dermatitis are considered hyper-reactors who have impaired essential function of the skin barrier, especially the skin barrier of the perioral region, characterized by thin permeable stratum corneum and imbalance of intercellular lipids, which makes them more susceptible to various internal and external irritants that contribute to the development of the disease. The verification of this connection reinforces the need for clinicians to address this issue when approaching their patients and formulating the best treatment plan. Treatment should emphasize repairing the impaired skin barrier function to minimize associated skin inflammation and sensitivity, which results in resolution of the objective and subjective symptoms.

KEY WORDS: skin barrier, periorificial dermatitis, perioral dermatitis, transepidermal water loss, corticosteroids

INTRODUCTION

Periorificial dermatitis (PD) is a benign inflammatory facial dermatosis presenting in both children and adults as persistent grouped tiny erythematous papules, papulovesicles, and papulopustules sometimes on the background of pink, scaly patches (1,2). Although its most common form is perioral with characteristic spared skin zone around the vermilion border, there can be additional or exclusive periocular and perinasal involvement, which is the reason why the term periorificial dermatitis is used (3). Patients frequently complain of subjective symptoms like burning or stinging and/or pruritus. The disease is increasing in its incidence but still presents a challenge

for physicians when it comes to etiology, pathophysiology, and appropriate therapy. Several etiopathogenetic factors have been proposed, but none of these fully explains the intricate pathogenesis of the disease (4-7). In addition to the most well-known contributing factor, topical corticosteroids (TC) (8), several other factors have been proposed including excessive skin cleaning and washing, occlusive skin moisturizers, physical sunscreens and cosmetic products, fluoridated toothpastes, fusobacteria, *Candida albicans*, *Demodex folliculorum*, and hormonal influences dependent on the menstrual cycle or oral contraceptive therapy (1,9-13).

It is currently believed that the interplay of both intrinsic and extrinsic factors is crucial for the development of PD, with an emphasis on the interaction of external irritants, atopic diathesis, and deficient skin barrier (SB) function (1,9,14,15). Deficiencies in SB function and features of atopy have been detected at increased frequency in patients with PD (14-16), so it is believed that impaired SB function could augment the risk of persistent cutaneous inflammation after exposure to external and internal irritants, but its definitive role has not been established yet.

In order to corroborate the previously proposed role of SB in PD, we conducted a clinical review on the state of the SB in PD and its proposed role in the etiopathogenesis of the disease as well as the factors influencing SB function which result in occurrence or worsening of PD. Four databases, EMBASE, SCOPUS, MEDLINE (PubMed), and Google Scholar were thoroughly searched using the following key terms: "periorificial dermatitis", "perioral dermatitis", "periocular dermatitis", "skin barrier", and "corticosteroids". The selection process was performed through an initial screening of titles and abstracts, followed by evaluation of full-text articles. Further papers were also identified from the reference lists of the above-retrieved papers and citations, as identified by Web of Science.

The function of skin barrier defects in most common inflammatory facial skin disorders – atopic dermatitis and rosacea

The skin is both a physical, "chemical", and immunological antimicrobial barrier that has a critical role in the prevention of water loss, preservation of electrolyte balance, allergen penetration, and host defense against microbial invasion (17). The main component of the SB is the multilayered *stratum corneum* (SC), often modeled as a brick wall because of its filmogenic features due to SC corneocytes with their resistant cell envelopes and keratin microfibrils that produce a physical barrier of a cross-linked matrix containing various proteins and multiple lamellar sheets enriched in ceramides, cholesterol and free fatty acid (18,19). Nucleated cells with a cytoskeleton and tight and gap junctions contribute to the physical barrier. Filaggrin (FLG) and proteins of the tight junctions (TJs) (occludin, claudin, zonula occludens 1 and 2, junctional adhesion molecule-1, and multi-PDZ-1) have been the most studied components of the SB (20-23). FLG, after being hydrolyzed, contributes to the formation of relevant components for pH maintenance, moisture, and skin protection against microbial agents (24-26). TJ proteins with active

expression, on the other hand, are important to control the selective permeability of the epidermis to form the barrier against the external influences (20,27,28). The "chemical" barrier is formed by lipids, the "acid mantle", antimicrobial peptides (AMPs) secreted by keratinocytes, mast cells (MCs) and sebocytes, and the FLG that aggregates keratin filaments and produces natural moisturizing factors (NMF) (19,29). These components synergistically ensure proper keratinization and lipid synthesis, providing antimicrobial protection and adequate skin hydration.

An intact SB can be regarded as the first and most essential component of the innate immune system (17). It is well-known from various studies, mostly examining atopic dermatitis (AD), that the impairment of the SB function, which corresponds to increased transepidermal water loss (TEWL) (30) and decreased SC hydration, is correlated to initiation of a cytokine cascade in the human skin (24,29,31,32), which supports the claim that dysfunction of SB greatly contributes to triggering and perpetuation of inflammation in the affected skin. Patients with AD and deficiency in FLG expression have decreased SC hydration, increased TEWL, higher pH which causes impaired serine protease activation and modification of microbiome, impaired skin integrity due to reduced protein expression in keratinocytes, and impaired AMPs function which leads to ongoing inflammation that contributes to already impaired SB function (29,33). It is not only in AD, but also other inflammatory dermatoses such as rosacea, that increased basal TEWL activates certain epidermal proteases, specifically SC serine proteases, and this activation leads to inflammation (15,16,34-36).

Not all patients with AD can attribute their disease to FLG mutations; in such patients we can detect other causes of the impaired barrier, mostly altered composition and structure of the lipids (37-42). Skin lipids produced by sebaceous glands not only contribute to integrity, but also exhibit strong antimicrobial activity (43). In addition to the FLG mutations and lipid disbalance, there are numerous factors which can be influenced and whose functions can be altered, since many proteolytic enzymes and protease inhibitors are involved in obtaining the normal function and structure of the barrier. We can say that all the important functions of the barrier are a result of the barrier's structure and organization. Except for genetic predisposition, where FLG mutation has the central role, many exogenous and endogenous stressors can additionally compromise SB, such as psychosociological stress, environmental pollution, and hygiene products/cosmetics which cause further damage to the SB (29,35,44-47).

In rosacea, as one of the most common facial dermatoses that is being clinically correlated to PD according to some authors, studies assessing SB are scarce and they focus mostly on sebum production (48). Two studies reported that rosacea depends more on skin hydration levels, with dry skin being affected the most, than on the amount of sebum (49,50). Surprisingly, there is data that supports evidence that sebum production is important but due to the content itself, particularly of fatty acids, which may influence the SB integrity of patients with rosacea (51).

Rosacea has a complex pathophysiology characterized by a modified innate immune response to environmental stimuli (52,53). Under normal physiologic conditions, triggering the innate immune system leads to controlled increases in AMPs (e.g. cathelicidins, defensins, psoriasins) and cytokines in the skin (54,55). These pathways are disrupted in patients with rosacea who have been shown to have increased baseline expression of AMP cathelicidin and serine protease kallikrein 5 (KLK5) that cleaves cathelicidin into its active peptide form – cathelicidin LL-37 (Cath LL-37), which possesses proinflammatory and angiogenic properties by promoting leukocyte chemotaxis and angiogenesis (56-59). Although mostly attributed to the pathophysiology of rosacea, Cath LL-37 is, along with other overexpressed AMPs, also implicated in the pathogenesis of AD and psoriasis (55,60,61). Not only is KLK5 increased in rosacea pathology, but there is also an increase in molecules that activate it and promote inflammation, i.e. Toll-like receptor 2 (TLR2) and matrix metalloproteinases (MMPs) (62-64). Zheng *et al.* (65) showed that Cath LL-37 also stimulates the generation of reactive oxygen species (ROS); their importance in rosacea pathophysiology is emphasized by the effectiveness of the most commonly used topical agent in the treatment of rosacea and PD – metronidazole (66). Cath LL-37 has emerged as a key mediator in the pathogenesis of rosacea after being examined in animal studies, which showed that intradermal administration of Cath LL-37 induces an inflammatory response with rosacea-like features (56). Doxycycline, which is a proven and effective treatment for both rosacea and PD, directly inhibits MMP-9 which in turn inhibits KLK5 activity, suppresses activation of cathelicidins in human epidermal keratinocytes, and results in suppression of inflammation and clinical improvement (67,68).

MCs which are well-known as one of the cells responsible for secretion of AMPs, have recently been identified as key mediators of cathelicidin-initiated skin inflammation in rosacea (69-71). MCs, MC proteases, and MMP-9 are found in increased numbers in the skin of patients with rosacea. It is known that this

cell type partly regulates SB function, not only by being the primary source of Cath LL-37 responsible for the inflammation and worsening of the SB but also by acting through its proteases responsible for vasodilatation and angiogenesis as well as amplification of the inflammation by recruitment of other immune cells, primarily neutrophils (69,72). The most abundant MCs mediator is tryptase, which causes direct proteolytic damage, activates proteinase-activated receptors and neuropeptides precursors, and causes inflammation. MCs are rich in proinflammatory mediators, particularly tumor necrosis factor and IL-6, which could also perpetuate local inflammatory processes in response to chemical, mechanical, psychological, or oxidative stress (72).

The impairment of the skin barrier in periorificial dermatitis

As mentioned previously, current understanding of the etiopathogenesis of the PD points to the importance of skin-environmental interactions with an emphasis on the interaction of external irritants, atopic diathesis, and impairment of SB function (73). The clinical observation of a tight association of PD with sensitive skin has led scientists to the concept of abnormal epidermal barrier function in PD that is in contrast to AD restricted only to facial skin, with both clinically involved and uninvolved areas of the facial skin having SB impairment, mostly the perioral region, suggesting the presence of mild invisible inflammation (15,74). A Japanese group of authors conducted a study to evaluate differences in biophysical functions of skin in distinct facial regions (74). They showed that the barrier function of SC is significantly poorest on the chin, whereas the nasolabial fold region presented with the highest TEWL, in contrast to the cheek region presenting with the lowest TEWL. Furthermore, the corneocytes on the chin and the nasolabial folds were smaller than those on the cheeks but increased in size with age, which is in concordance with results showing a decrease in TEWL. The group also tried to characterize the skin surface lipids on facial specific sites. They revealed that skin surface lipids were richest on the nose, forehead, and chin, significantly higher than those measured on the cheek, but they did not find a correlation between skin surface lipids and TEWL that would corroborate the evidence of reduced lipids in PD skin. Their results are similar those of Shiner and Maibach, demonstrating that the nasolabial skin is the most sensitive area of the face when exposed to certain irritants (75). It is therefore understandable that patients with impaired facial SB are hyper-reactors because of the thin permeable SC which makes them

more susceptible to chemical irritations, namely that of the perioral region, leading to the development of PD (76,77). Although patients with impaired facial SB are considered to be hyper-reactors, and the important feature of many "hyper-reactive" skin diseases is mounting of excessive immune cell response to low-level stimuli (78), there are still no studies focusing on the immune dysfunction in PD, either in the skin or systemically. Skin of rosacea-prone persons and patients presenting with sensitive skin both have in common perpetuation of perivascular, epidermal, and dermal inflammation which synergistically accelerates epidermal proliferation and differentiation, resulting in functionally impaired SC without the ability to maintain proper hydration. This leads to hydration loss and increased TEWL, which is already increased by the underlying inflammation. As explained previously, similarly as in AD, in addition to increased TEWL certain epidermal proteases are being activated and there is a change in the innate immune functions, including an increase in AMPs that leads to ongoing inflammation. It is possible that dysregulation of the innate immune system, very similar to the one involved in rosacea and AD, is the core pathogenetic pathway that augments the risk for persistent skin inflammation in patients with PD who already have impaired SB and features of atopy and who are exposed to external stressors/irritants.

Since skin lipids are crucial for a healthy skin barrier (38,79), we tried to find articles presenting direct evidence of reduced lipids in PD skin, but there were no studies that examined at least one component crucial for SB function in this group of patients. Paradoxically, there were studies showing that excessive use of moisturizers, especially occlusive moisturizing emollients based on paraffin or petrolatum jelly, can be irritating for the facial skin and result in SB dysfunction, leading to edema of the SC and increased TEWL, leading to the conclusion that the skin lipids content and the structure is more important than the quantity itself (9,15). An Australian study conducted by Malik corroborated the role of excessive topical cosmetics usage in the development of PD by demonstrating that a combination of moisturizer, night cream, and foundation significantly increases the risk of PD (80). Dirschka *et al.* (14) investigated facial SB function and various markers of atopy to elucidate their role in the development of PD. On the basis of their findings, they proposed that atopy serves as an intensifier that contributes to ongoing inflammation in PD after non-specific irritants have induced impaired SB function. Unfortunately, despite some minor investigative and clinical studies, there are currently no studies or evidence that would corroborate the role of SB function

in PD pathogenesis by elucidating specific molecular or genetic pathways. Established link between SB dysfunction and the cutaneous cytokine cascade explained in detail in AD pathogenesis (29,32) has not been studied in PD, although deficiencies in SB function and features of atopy have been detected in the majority of patients with PD.

Topical steroids – skin barrier – periorificial dermatitis

It is well-known that TC use triggers or aggravates PD, and therefore it should be avoided as much as possible when dealing with this group of patients. It is not only TC usage, but also the use of inhaled or nasal corticosteroids, and even the "connubial" exposure from intimate contact with another person who uses TC that can result in the disease (12).

Since their first introduction in 1951, the abuse of the TC has been a prevalent problem. Although it is strongly suggested to avoid prolonged continuous and/or repeated intermittent TC use in disorders like PD and rosacea, these instructions are often not adhered to by the patients (81). Initial improvement of their symptoms with TC treatment leads to prolonged misuse and long-term dependency on TC that result in adverse effects such as epidermal atrophy, degeneration of dermal structure, and collagen deterioration that are predictable but difficult to manage (82,83). Both human and animal model studies showed various cutaneous abnormalities that occurred as a result of TC use, including alterations in epidermal structure and SB permeability that lead to increased TEWL (8,37,84). When we translate these findings into clinical practice, we often see that the routine misuse of fluorinated TC on the face results in a large group of skin complications like PD and an eruption clinically indistinguishable from rosacea – "steroid-induced rosacea" – which is also known in literature under the term corticosteroid-induced rosacea-like dermatitis (CIRD) (34,82). CIRD was reported by Del Rosso to occur more commonly in female patients (72%), often with a history of atopy (67%), and the patients additionally reported symptoms such as burning, stinging, dryness, and pruritus (34). It is believed that anyone may develop this complication; however, it may be that rosacea-prone persons and persons with sensitive skin or history of atopy are more susceptible, which could be explained by the fact that both the facial skin of these group of patients and those who had been treated with TC have essentially impaired epidermal barrier (15,85). In patients prone to rosacea, with chronic TC use PD may eventually progress into a more severe granulomatous subtype

of the disease occurring in the same distribution as flesh-colored to erythematous or yellow-brown papules (5,86,87). It is believed that TC cause damage of the hair follicle wall followed by edema in the follicle cells, which results in the development of granulomatous PD (62,87). When examining the medical history of most patients in our clinical practice, we often came across prolonged continuous and/or repeated intermittent TC use. Initially, inflammation was suppressed with TC, but the eruption recurred upon the withdrawal of the TC. According to medical history, most of our patients with PD that were mistreated with TC over a longer period had atopic dermatitis, seborrheic dermatitis, and sometimes rosacea (1). As it is usually observed in patients with PD and CIRD, we noticed extreme sensitivity of our patients' facial skin resulting from perturbed epidermal permeability, caused by both underlying disease, excessive skin cleaning, and prolonged TC use.

Stress – skin barrier – periorificial dermatitis

Stress is a term which has become ubiquitous in the everyday life of each and every one of us and presents a burden to our normal functioning. Psychological stress is triggered by a stimulus that induces a reaction in the brain which consequently activates additional physiological systems in the body, including the nervous, endocrine, and immune system (88,89). There is more and more evidence and studies corroborating the concept of neuro-endocrine skin that was formulated twenty years ago, which sees the skin as a bi-directional platform for signal exchange with other peripheral organs, such as the endocrine and immune system (88,90,91). On the other hand, the skin allows the brain to achieve rapid and selective responses to the environment in order to maintain local and systemic homeostasis. The skin represents the first line of defense against many external irritants and noxious inputs, being especially sensitive to psychological stress according to many investigators. Studies have demonstrated that psychological stress alters the homeostasis of the cutaneous barrier as well as the adaptive immune system, which is even clearer in studies showing reduced recovery time of the SC after elimination of psychological stress (92-95). Choi *et al.* (94) investigated the influence of psychological stress on SB homeostasis and showed that, similarly to glucocorticoids, it alters SB homeostasis and SC integrity and inhibits epidermal lipid synthesis, resulting in decreased production and secretion of lamellar bodies and impaired production of lamellar membranes in SC interstices. They also found that topical treatment with physiologic lipids restores both permeability barrier homeostasis and SC integ-

rity even in situations of ongoing psychological stress, which means that topical treatment with lipids could be beneficial in stress-induced, barrier-associated dermatoses.

Antigen presentation by epidermal Langerhans cells has also been altered under the influence of stress (96). It is therefore not surprising that many dermatological diseases are triggered or exacerbated by psychological stress. Stress signals initiate the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system, induce secretion of different neurotransmitters, cytokines, and hormones that possess skin receptors, and can aggravate skin diseases like acne, psoriasis, atopic dermatitis, rosacea, and even PD (45,97-99). The exact mechanisms of stress-induced triggering or aggravation of PD have not yet been clarified. We hypothesize that glucocorticoids and adrenal androgens which are released during emotionally stressful periods lead to skin hyper-sensitivity to various other stimuli but also provoke or sustain inflammation through activation of an impaired epidermal barrier-initiated cytokine cascade and AMPs disbalance. The influence of psychological stress on SB function, just as the influence of endogenous glucocorticoids, could be connected to the inhibition of epidermal lipid synthesis resulting in decreased production of epidermal lamellar bodies. Because one of the functions of human epidermal lamellar bodies is to deliver endogenous lipids, AMPs, and desquamatory enzymes to SC interstices, a decrease in its formation contributes to an impairment of the antimicrobial SB function which explains the uncontrolled inflammatory response when such skin is exposed to various external irritants, especially infectious agents (93,100). Based on results in the field of neuroimmunology showing that MCs are highly sensitive to modulation of stress hormones such as corticotropin-releasing hormone (CRH) and ACTH, there is increasing evidence that MCs have a functional role as "switchboards" of neurogenic inflammation during stress responses (72,91).

MANAGEMENT

The diagnosis of PD is established clinically based on physical examination and clinical history. Although the diagnosis is straightforward in most cases, sometimes a biopsy is helpful to exclude other differential diagnoses like sarcoidosis, granulomatous rosacea, allergic contact dermatitis, or a variety of cutaneous adnexal neoplasms (101). Because of the perturbed SB of the affected facial skin, it is suggested to perform a "null therapy" or "zero therapy" approach for the first few weeks of treatment as a way to prime the skin (34,102). During this period, all topical products

should be discontinued, including topical medications, cosmetics, soaps, astringents, abrasives, and occlusive moisturizers. If the history is positive for TC misuse, the most important step in the treatment is to immediately cease their application either abruptly or by tapering them down by using a low potency TC such as 1% hydrocortisone, or by slowly tapering the frequency of more potent TC application prior to their cessation (12,73). After subsequently priming the skin, usually just with saline or chamomile tea dressings along with a non-occlusive moisturizing emulsion, other beneficial therapeutic options which result in excellent therapeutic response should be introduced. Several topical options have been suggested as first-line pharmacologic agents for PD – metronidazole 0,75% gel or 1% cream, 2% erythromycin gel, clindamycin gel or lotion, topical sulfur preparations, azelaic acid, and calcineurin inhibitors, mostly 1% pimecrolimus cream, especially when it comes to treatment of CIRP or PD induced or exaggerated by TC (5,34,73,103,104). However, some patients, mostly those with TC-induced PD, complain of irritation after starting topical medication, in which case the period of “null therapy” should be prolonged. In our clinical practice, we have had excellent results by applying

this approach, which is seen in the example of a typical patient with PD presenting with a periorcular variant of PD (Figure 1, a, b).

In cases of extensive presentation of PD or if topical therapy is not enough or not helpful (we usually wait up to one month of application twice a day) systemic treatment with oral antibiotics is suggested (5). The most commonly used antibiotics for PD are tetracyclines because of their anti-inflammatory properties, but oral erythromycin is used as an alternative for patients who cannot tolerate tetracyclines or for children under age of nine due to the risk of adverse effects (1,73). When both topical therapy and oral antibiotics fail to yield the desired result, low-dose isotretinoin can be used with good response (105,106). There is more and more evidence of beneficial and well-tolerated treatment of PD with either oral or 1% topical ivermectin in individual cases, but well-designed prospective studies with larger number of patients are needed to corroborate its therapeutic role in PD (107).

Most of our patients confirm that PD has a strong negative impact on their quality of life through stigmatizing feelings and anxiety. They report that their facial skin condition negatively influences their emotional health, which results in psychological comorbidities such as anxiety disorders and social phobias. There is no doubt that this emotional stress aggravates the underlying disease even more. Therefore, management and therapeutic approach of PD should be adjusted individually, with special attention to triggering factors, the irritant potential of topical therapeutics, patient education in the disease course, and continuous psychological support, which results in improved quality of life and better social functioning of our patients.

CONCLUSION

As intact SB is synonymous for healthy skin, it is not surprising that SB function has often been examined many times when studying various inflammatory dermatoses. Although some parts of the puzzle are still missing, there is more clinical and observational evidence that even PD can be triggered or exacerbated through disruption of SB permeability and function. There is also more evidence that patients with PD are hyper-reactors with impaired essential SB function, especially SB of the perioral region, characterized by thin permeable SC and imbalance of intercellular lipids which makes them more susceptible to various internal and external irritants and leading to the development of PD. Unfortunately, there are still no scientific studies which would further explain the



Figure 1. Periorcular presentation of periorificial dermatitis in a 45-year-old female patient. **(a)** Topical corticosteroid-induced worsening of periorcular dermatitis presenting as clustered monomorphous erythematous papules along with stinging sensation; **(b)** Marked initial improvement noted at two weeks after cessation of topical corticosteroids, treatment with a ceramide-based gentle cleanser, wet saline dressings, a non-occlusive moisturizing emulsion, and 1% metronidazole cream applied once daily.

exact intrinsic factors that cause changes in the SB in patients with PD or the specific genetic and molecular pathways responsible for the inflammation of specific facial localizations in affected individuals. More research in this area would corroborate the role of SB dysfunction in PD and be useful in improving our understanding of the development of the disease. The validation of SB impairment in patients with PD reinforces the need for clinicians to address this issue when approaching patients with PD and formulating the best treatment plan. The treatment should emphasize repair of the impaired SB function and reduction of the increased TEWL in order to minimize associated skin inflammation and sensitivity. Treatment recommendations should be evidence-based, and the use of barrier-improving moisturizers should be encouraged because they shorten the treatment period needed for improvement and provide both sparing of other therapeutic agents and skin care maintenance quality.

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